SUPPORT FOR THE AMENDMENTS

Claims 46, 49, 51, 55, 56, 65, 66, and 67 have been amended as suggested by the Examiner. Claims 49, 51, and 66 have been amended to further clarify the subject matter thereof, and to place these claims in proper U.S. format. Claims 69-86 have been added.

Support for amended Claims 46, 49, 51, 55, 56, 65, 66, and 67 appears at least in the previous wording thereof. Newly added Claims 69-86 find their support at least in previous Claims 46-53, 55-63, and 65-68.

No new matter is believed to have been added to the present application by this amendment.

REMARKS

Claims 46-53, 55-63, and 65-86 are now pending. Favorable reconsideration is respectfully requested.

Applicants submit herewith drawings as required under 37 C.F.R. §1.85(a).

The rejection of Claims 56-63 under 35 U.S.C. §112, first paragraph, for lack of enablement, is respectfully traversed.

One skilled in the art, in view of the complete disclosure of the present invention and using common general knowledge in the field thereof, can realize and reproduce the invention as specified in amended Claims 56-63, for the following reasons.

Amended Claim 56 reads as follows: "a synthetic polynucleotide comprising a synthetic sequence encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein (MSP-1), wherein said synthetic sequence has a total GC content of 40% to 60%." Claims 57-63 are dependent upon Claim 56 and are thus directed to different aspects of this "synthetic polynucleotide."

Appropriate guidance is given in the specification to the skilled artisan, enabling that person to find out and select synthetic polynucleotides included in the scope of Claim 56. In fact, two essential features are recited in Claim 56, that determine the scope thereof. On the one hand, a functional definition is provided: "encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein 1 (MSP-1)." On the other hand, a structural definition is given: "a total GC content of 40% to 60%."

One skilled in the art, relying at least on native *Plasmodium falciparum* p19-encoding sequences (SEQ ID NO:3 and SEQ ID NO:6), can design synthetic polynucleotides expected to fulfill the definitions above, if necessary using computer programs for nucleotide sequence design and alignment. Applicants submit that this is routine procedure for the person skilled in the art.

Indeed, using routine laboratory tests, such as nucleotide sequencing, nucleotide sequence hybridization, and/or immunological assays using, for example, the monoclonal antibody that specifically recognizes the p19 protein from *P. falciparum* (deposited at the CNCM under No. I-1846), the person skilled in the art can check for both the functional and structural essential features that characterize the subject matter of Claim 56.

To do so, the skilled person can also rely on examples of synthetic sequences that are disclosed as meeting these structural and functional requirements in SEQ ID NO:1 (PfMSP1p19S, illustrated in Figure 1A), SEQ ID NO:4 (PfMSP1p19A, illustrated in Figure 1B), SEQ ID NO:7 (illustrated in Figure 1C), and SEQ ID NO.9 (illustrated in Figure 1D).

Therefore, Applicants submit that the presently claimed invention can be obtained by routine experimentation by the skilled artisan.

Thus, as stated by the Court in *Fields v. Conover*, 443 F2d 1386, 1390-1391, 170 USPQ 276, 279 (CCPA 1971):

> [A] disclosure complies with [§ 112] even though some experimentation, provided it is not an undue amount [and provided that it does not require ingenuity beyond that to be expected of one of ordinary skill in the art], is still required to adapt the invention to particular settings.

It should be noted that the test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible if it is merely routine. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'l 1986.)

Moreover, Applicants have added new Claims 76-83 which recite those particular constructs that comprise a synthetic sequence encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein 1 (MSP-1), wherein this synthetic sequence has a GC content of between 40% to 60%, i.e., the constructs contained in the baculovirus vectors deposited at the CNCM under Nos. I-1661 and I-1662.

Therefore, in view of the above, the claims are enabled. Accordingly, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 56-63 under 35 U.S.C. §112, first paragraph, as not complying with the written description requirement, is respectfully traversed.

The Examiner purports that "although describing, and being enabling for, particular constructs as found in the deposited viruses given CNCM registration numbers I-1659, I-1660, I-1661, I-1662, and I-1663, the specification does not reasonably provide description of or enablement for an invention of the scope as instantly claimed because one would not know, absent further description and guidance from applicant, what sequences or characteristics are intended as encompassed by a 'gene'."

Claim 56 has been amended, replacing the term "gene" with the expression --synthetic sequence--, which should obviate this rejection.

Applicants submit that, in the technical field of the present invention, a "gene" is known to be a nucleotide sequence that encodes an amino acid sequence. This nucleotide sequence can be either native or synthetic, i.e., recombinant. Native nucleotide sequences from *P. falciparum* are intentionally excluded from the scope of Claim 56 as not fulfilling the structural requirement of having a GC content of between 40% to 60%.

Furthermore, Applicants submit that the claimed sequences are inherently and adequately described to comply with the written description requirement of §112, first paragraph, by reference to deposits of five sequences that are within the scope of the claims. See *In re Enzo*, 01-1230 (Fed. Cir. July 15, 2002).

Therefore, in view of the foregoing, withdrawal of this rejection is respectfully requested.

The rejection of Claims 46-53 and 55-63 under 35 U.S.C. §112, second paragraph, is believed to be obviated by the amendment submitted above.

Claims 46-53, and 55 have been amended as suggested by the Examiner.

Also, Claims 56-63 have been amended as indicated above, by replacing in claim 56 the term "gene" with the expression --synthetic sequence--.

In view of these amendments, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 46, 48, 56, 58, 61, 65, and 66 under 35 U.S.C. §103(a) over the combined teachings of Chappel et al., Miller et al., and Longacre et al. is respectfully traversed.

In rendering this rejection, the Examiner asserts that "one would have expected many polynucleotides of the genus specifically encoding this known sequence of the antigenic *P. falciparum* MSP-1 protein C-terminal p19 fragment to function in baculovirus vectors as

taught by the combined references and would have had motivation to use any of the genus of encoding polynucleotides therefor."

Chappel et al. show that the first of the two epidermal growth factor (EGF)-like motifs in the 19-kDa fragment of the *P. falciparum* MSP-1 protein can be expressed as a fusion protein in *Escherichia coli*, and that it is a target for antibodies capable of inhibiting parasite invasion *in vitro*. Chappel et al. do not teach, disclose nor even suggest any modification of the GC content of the nucleotide sequence encoding the 19-kDa fragment of the *P. falciparum* MSP-1.

Miller et al. analyze MSP-1 sequences to identify polymorphic regions. To do so, sequences were aligned. These sequences were broken into blocks based on sequence homology and variability, and sequences of the seventeen resulting blocks were further analyzed. Miller et al. is silent with respect to the GC content of MSP-1 sequences.

Longacre et al. describe the production, in the baculovirus expression system, of recombinant 42- and 19-kDa C-terminal fragments of the *P. vivax* MSP-1 protein, either in a secreted or in a membrane-anchored form. To do so, the native sequences from the 42- and 19-kDa C-terminal fragments of MSP-1 from *P. vivax* were used. Longacre et al. do not teach, disclose nor even suggest any modification of the GC content of the nucleotide sequences encoding the 42- and 19-kDa C-terminal fragments of MSP-1 from *Plasmodium*.

In view of the prior art teachings and since all references are silent with regard to the GC content of the sequences of fragments of protein MSP-1, Applicants submit that it was not obvious to increase the GC content of a synthetic sequence, compared to the native *P. falciparum* sequence encoding a 19 kilodalton C-terminal fragment of MSP-1, to enhance expression thereof when using the baculovirus/insect cell expression system.

Thus, as stated in *In re Burt and Walter*, 148 USPQ 549 (CCPA 1966):

> [S]ilence in a reference is not a proper substitute for an adequate disclosure of facts from which a conclusion of obviousness may justifiably follow.

Furthermore, from the combined teachings of Chappel et al., Miller et al., and Longacre et al., one skilled in the art would know: (1) the nucleotide sequence of the MSP-1 protein from *P. falciparum*; (2) that the C-terminal portion corresponding to the 19-kDa fragment of MSP-1 is one of the most conserved regions between *P. vivax* and *P. falciparum*; and (3) that correctly folded MSP-1 protein fragments, retaining thus their native tertiary structure which is responsible for the protective response thereto due to conformational epitopes, can be obtained using the baculovirus/insect cell system with expression and secretion from the infected cell.

In consequence, the skilled artisan could have been encouraged by these combined teachings, only to adapt the disclosure of Longacre et al. to native sequences from the 42- and/or the 19-kDa C-terminal fragments of the MSP-1 protein from *P. falciparum*.

Therefore, at the time the application was filed, and since all references are silent with respect to the GC content of the sequences under consideration, the person skilled in the art could not find therein any suggestion nor any motivation to modify this GC content.

To establish a *prima facie* case of obviousness, "the prior art reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2142). In addition, if a reference needs to be modified to achieve the claimed invention, "there must be a showing of a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion." See *Sibia Neurosciences Inc. v. Cadus Pharmaceutical Corp.* 55 USP2d 1927 (Fed. Cir. 2000).

In this instance, there is no suggestion or motivation in any of the cited references to modify the GC content.

Moreover, since none of the cited references suggest or disclose increasing the total GC content of *Plasmodium* polynucleotides encoding products exhibiting an antigenic activity of interest for vaccination purposes, it appears that the Examiner has maintained this rejection through hindsight reproduction. Nevertheless, hindsight reproduction of an invention is forbidden by the Federal Circuit, as stated in *In re Pleuddemann*, 910 F2d 823, 828, 15 USPQ2d 1738, 1742 (Fed. Cir. 1990):

> It is legal error to use "[an inventor's patent]" specification teaching [of both a novel and nonobvious compound and methods of using that compound] as though it were prior art in order to make claims to [the] methods [of use] appear to be obvious.

Hence, no matter whether the skilled artisan would have expected, due to genetic code degeneration, many polynucleotides to encode products having the antigenic properties of the p19 *P. falciparum* protein fragment. Modifying the GC content of polynucleotides encoding products displaying these antigenic properties was not obvious in view of the cited references at the time the application was filed.

Furthermore, Applicants submit that, in maintaining this rejection, the Examiner has relied an another legally forbidden evaluation of the claims, i.e., an "obvious-to-try" standard. Indeed, as stated in *In re Eli Lilly & Co.*, 92 F2d 943, 945, 14 USPQ2d 1741, 1743 (Fed. Cir. 1990):

> An "obvious-to-try" situation exists when a general disclosure may pique the scientist's curiosity, such that further investigation might be done as a result of the disclosure, but the disclosure itself does not contain a sufficient teaching of how to obtain the desired results, or that the claimed result would be obtained if certain directions were pursued.

Indeed, admitting, for the sake of argument, that the person skilled in the art could in theory have the idea of modifying the GC content of nucleotide sequences in order to enhance their expression when using the baculovirus/insect cell expression system, that person would not find in any of the cited references, even combined, appropriate guidance to

find out the conditions for achieving this purpose. Indeed, without any description of experiments enabling this goal to be reached, that person would necessarily have to: (i) design experimental procedures; (ii) do many tests and assays to refine said procedures; and (iii) adjust and finalize them to solve unexpected problems. This obviously goes beyond routine work, takes time, requires inventive ingenuity, and requires an undue burden of efforts. Moreover, the skilled artisan would not be certain of having any reasonable chances of success.

Finally, to clarify the record, the Examiner purports that "it is not clear that the range of total G+C alone can be used as predictive of an unobvious enhanced expression in a baculovirus vector, as the specific sequence shown to be expressed by applicant was apparently modified based upon preferred codon usage in Sf9 cells and not merely upon G+C content."

Applicants dispute these arguments for the following reasons.

Applicants submit that the GC content and the preferred codon usage for gene expression in a given type of cells are two correlated concepts. Indeed, if one bases nucleotide sequence alterations on the preferred codon usage in a given cell, one will necessarily modify thereby the ratio between the four constitutive bases A, T, G, and C in said sequence. Consequently, the ratio A+T versus G+C will also be changed. Hence, the total GC content of the altered nucleotide sequence will be modified. Reciprocally, if one changes some bases in a nucleotide sequence to increase or decrease the GC content thereof, this will have an effect, either positive or negative, on the capacity of the transcription/translation cellular machinery to express the resulting sequence, because of the preferred codon usage in the cell.

In conclusion, Applicants submit that the Examiner has not met the burden of proving a *prima facie* case of obviousness according to the proper legal standards. Therefore, in view of the above, withdrawal of this rejection is respectfully requested.

Claim 67 has been objected to as being dependent upon a rejected base claim.

This claim has been amended according to the Examiner's suggestion, in an independent form that includes all of the limitations of Claims 65 and 66. This should obviate the objection to this claim.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
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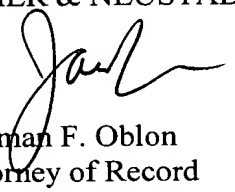

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Amendment Filed on Herewith:

IN THE CLAIMS

--46. (Thrice Amended) A baculovirus vector comprising a promoter, a synthetic polynucleotide encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein 1 (MSP-1), wherein said synthetic polynucleotide has a GC content of 40% to 60%, and a polynucleotide encoding a signal peptide of a *Plasmodium* MSP-1 protein.

49. (Thrice Amended) The baculovirus vector of Claim 48, wherein said glycosylphosphatidylinositol anchor coding sequence is from a CD59 gene or a CD14 gene.

51. (Twice Amended) The baculovirus vector of Claim 46, wherein said synthetic polynucleotide and said polynucleotide encoding a signal peptide comprise[s] SEQ ID NO:7.

55. (Thrice Amended) A baculovirus vector selected from the group consisting of PfMSP1p19A deposited at the CNCM under No. I-1661, PfMSP1p19S deposited at the CNCM under No. I-1662, and PcMSP1p19S deposited at the CNCM under No. I-1663.

56. (Thrice Amended) A synthetic polynucleotide comprising a [gene] synthetic sequence encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* merozoite surface protein 1 (MSP-1) [polypeptide], wherein said [polynucleotide] synthetic sequence has a total GC content of 40% to 60%

65. (Twice Amended) A baculovirus vector comprising a promoter, a synthetic polynucleotide encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum*

merozoite surface protein 1 (MSP-1) having a GC content of between 40% to 60%, and a polynucleotide encoding a signal sequence of a *Plasmodium vivax* MSP-1 protein.

66. (Twice Amended) The baculovirus vector of Claim 65, wherein said synthetic polynucleotide [sequence] further comprises a glycosylphosphatidylinositol anchor coding sequence.

67. (Twice Amended) [The] A baculovirus vector, [of Claim 66, wherein said] comprising:

(a) a promoter;

(b) a synthetic polynucleotide comprising a synthetic sequence encoding a 19 kilodalton C-terminal fragment of a *Plasmodium falciparum* rnerozoite surface protein 1 (MSP-1) having a GC content of between 40% to 60%, and a glycosytphosphatidylinositol anchor coding sequence [is] from a CD59 gene or a CD14 gene; and

(c) a polynucleotide encoding a signal sequence of a *Plasmodium vivax* MSP-1 protein.

69-86. (New).--